PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference 544922000340	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/US2004/001146	International filing date *(day/month/year)* 16 January 2004 (16.01.2004)	Priority date *(day/month/year)* 17 January 2003 (17.01.2003)]
International Patent Classification (IPC) or national classification and IPC [7] A61K 31/70, G01N 33/567, C12Q 1/06		
Applicant THRESHOLD PHARMACEUTICALS, INC.		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 22 July 2005 (22.07.2005)
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Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
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PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing (*day/month/year*)	01 MAR 2005
Applicant's or agent's file reference 544922000340	FOR FURTHER ACTION See paragraph 2 below

International application No.	International filing date (*day/month/year*)	Priority date (*day/month/year*)
PCT/US04/01146	16 January 2004 (16.01.2004)	23 January 2003 (23.01.2003)

International Patent Classification (IPC) or both national classification and IPC

IPC(7): A61K 31/70; G01N 33/567; C12Q 1/06 and US Cl.: 514/23, 24, 25, 449; 435/7.21, 39, 40.51

Applicant

THRESHOLD PHARMACEUTICALS, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I — Basis of the opinion
- ☐ Box No. II — Priority
- ☒ Box No. III — Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV — Lack of unity of invention
- ☒ Box No. V — Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI — Certain documents cited
- ☐ Box No. VII — Certain defects in the international application
- ☐ Box No. VIII — Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(*b*) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US04/01146

Box No. I Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This opinion has been established on the basis of a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

☐ a sequence listing

☐ table(s) related to the sequence listing

b. format of material

☐ in written format

☐ in computer readable form

c. time of filing/furnishing

☐ contained in international application as filed.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US04/01146

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 7-14 are unsearchable as improper multiple dependent claims have been found to be unsearchable under Article 17(2)(b) because of defect under Article 17(2)(a) and therefore have not been included with any invention .

because:

☐ the said international application, or the said claim Nos. ____ relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 7-14 are so unclear that no meaningful opinion could be formed *(specify)*:

are unsearchable as improper multiple dependent claims have been found to be unsearchable under Article 17(2)(b) because of defects under Article 17(2)(a) and therefore have not been included with any invention.

☐ the claims, or said claims Nos. ____ are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claims Nos. ____

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form
- ☐ has not been furnished
- ☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details.

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
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Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has:
   - ☐ paid additional fees
   - ☐ paid additional fees under protest
   - ☒ not paid additional fees
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
   - ☐ complied with
   - ☒ not complied with for the following reasons:

   See the lack of unity section of the International Search Report(Form PCT/ISA/210)

4. Consequently, this opinion has been established in respect of the following parts of the international application:
   - ☐ all parts.
   - ☒ the parts relating to claims Nos. 1-6 and 15-20

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US04/01146

Box No. V Reasoned statement under Rule 43 *bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims 1-6 and 15-20	YES
	Claims None	NO
Inventive step (IS)	Claims None	YES
	Claims 1-6 and 15-20	NO
Industrial applicability (IA)	Claims 1-6 and 15-20	YES
	Claims None	NO

2. Citations and explanations:

Please See Continuation Sheet

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US04/01146

Supplemental Box
In case the space in any of the preceding boxes is not sufficient.

V. 2. Citations and Explanations:

Claims 1-6 and 15-20 lack an inventive step under PCT Article 33(3) as being obvious over Palazzo et al in view of Grima et al. The prior art of Palazzo et al teaches the use of substituted 1-benzyl-1H-indazole-3-carboxylic acids and derivatives thereof which is known as lonidamine and its analogs as pharmaceuticals which are administered in a single oral dose provoking a neat atrophy of the seminal line of the testes without causing other toxic effects. Thus, clearly suggesting that an energolytic agent such as lonidamine could treat/decrease the size of benign prostatic hyperplasia (BPH) which is a disease wherein prostate epithelial cells grow abnormally and block urine. Further, the secondary reference of Grima et al discloses reversible inhibition of spermatogenesis in rats by administering effective amount of lonidamine which resulted in morphological changes within the columnar epithelia cells in prostate in comparison to the control, wherein the epithelial cells surrounding the lumen were decreased in height and were less convoluted than the control as evidenced in Figure 4, B versus A.

The cited references are silent with respect of administering energolytic agent such as lonidamine to a human subject. However, it would be obvious to one of ordinary skill in the art at the time the invention was made to administer energolytic agent such as lonidamine to human subject because the prior art of Palazzo et al states that as a result of experiments on rat and monkeys, the product should be administered to a man orally at daily dose range of from 0.2 to 3 grams of the active compound. These compounds exhibit excellent intestinal absorption in man. Thus, in view of the above, one of ordinary skill in the art would be able to determine what dosages are effective, and what the optimal time frames would be for administration of lonidamine which is known in the art to be effective in combination therapy in the treatment of cancer. Thus, the instant application is seen to be optimization of art recognized methods, and is seen to be within the purview of skilled artisan.

Therefore, in view of the above, and in view of the combined teachings of the prior art, one of ordinary skill in the art would have been motivated at the time the invention was made to use the already known method for treatment or prevention of benign prostatic hypertrophy/hyperplasia that inhibits glycolysis and interferes with energy metabolism in prostate epithelial cells by administering a compound of an energolytic agent such as lonidamine. Thus, the teachings of the prior art renders obvious the instant invention as claimed in claims 1-6 and 15-20.

Claims 1-6 and 15-20 meet the criteria as set forth by PCT Articles 33(2) and 33(4).

Claims 1-6 and 15-20 lack an inventive step under PCT Article 33(3) as being obvious over Shidaifat et al in view of Chang et al. The prior art of Shidaifat et al teaches the effect of energolytic agent such as gossypol (GP) on the growth of prostatic cells from human benign prostatic hyperplasia (BPH) patients *in vitro*. GP also acts a potent inhibitor of cultured human BPH cell growth as assessed by thymidine incorporation assay. The results show that GP treatment resulted in a marked elevation of TGF-β_1 gene expression indicating that TGF-β_1 might be involved at least in part in the inhibitory pathway that is initiated by GP as shown in Figure 1. Thus, the reference suggests that GP as possible therapeutic agent for the prevention of human BPH. Therefore, this study was aimed to examine the effect of GP on the growth of human BPH cells. The prior art concludes by stating that these data indicate clearly the potential of GP for treatment of prostatic diseases. In human subjects, GP has been used as an effective male contraceptive agent and has been suggested for use as a possible therapeutic agent for the treatment of metastasis adrenal cancer with relative safety

Supplemental Box
In case the space in any of the preceding boxes is not sufficient.

and well tolerated side effects. In light of these findings, GP could be a potent chemotherapeutic agent against human androgen-dependent and -independent prostatic diseases.

Further, the secondary reference of Chang et al describes investigation of an energolytic agent such as gossypol's mechanism of action using canine prostate model of BPH. The investigation support the notion that gossypol (GP) can inhibit prostate cell proliferation and may be a potential therapeutic agent for use in controlling overgrowth of the prostate. The reference states that GP is known to bind to mitochondrial fractions and is uncoupler of oxidative phosphorylation, inhibiting respiration and ATP production and concludes by stating that GP posses significant potential for clinical use, alone or in combination with other therapeutic agents, as a regulator of cell growth in patients with BPH or prostate cancer.

The cited references are silent with respect of administering energolytic agent such as GP to a human subject. However, it would be obvious to one of ordinary skill in the art at the time the invention was made to administer energolytic agent such as GP to human subject because the prior art of Shidaifat et al teaches the effect of energolytic agent such as gossypol (GP) on the growth of prostatic cells from human benign prostatic hyperplasia (BPH) patients *in vitro* . Thus, it is within the skill of the art to use *in vitro* human data for *in vivo* human application. Therefore, in view of the above, one of ordinary skill in the art would be able to determine what dosages are effective, and what the optimal time frames would be for administration of GP which is known in the art to be effective in combination therapy in the treatment of cancer. Thus, the instant application is seen to be optimization of art recognized methods, and is seen to be within the purview of skilled artisan.

Therefore, in view of the above, and in view of the combined teachings of the prior art, one of ordinary skill in the art would have been motivated at the time the invention was made to use the already known method for treatment or prevention of benign prostatic hypertrophy/hyperplasia that inhibits glycolysis, impairs mitochndrial function, or otherwise interferes with energy metabolism in prostate epithelial cells by administering a compound of an energolytic agent such as GP. Thus, the teachings of the prior art renders obvious the instant invention as claimed in claims 1-6 and 15-20.

Claims 1-6 and 15-20 meet the criteria as set forth by PCT Articles 33(2) and 33(4).